Synthetic Methods

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Asymmetric Vinylogous Diels–Alder Reactions Catalyzed by a Chiral Phosphoric Acid**

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Abstract: *An unprecedented way to extend the synthetic utility of the Diels–Alder reaction to include a vinylogous reactivity space is described. A commercially available chiral phosphoric acid catalyst effectively activates cyclic 2,4-dienones towards a vinylogous [4+2] cycloaddition with 2-vinylindoles, which leads to stereochemically dense tetrahydrocarbazoles. The reaction proceeds with a high level of remote stereocontrol and exclusive chemoselectivity for the more distant double bond of the dienone.*

The Diels–Alder (DA) reaction is among the most powerful methods for the rapid and predictable construction of stereochemically dense cyclohexenyl rings.[1] Research that is aimed at further expanding the synthetic potential of the DA approach is still fascinating the chemical community. Avenues for new progress have mainly been provided by the emergence of asymmetric catalytic variants[2] and the desire to identify unprecedented diene–dienophile combinations. In contrast, the use of DA chemistry to stereoselectively shape the reactivity space that is remote from the catalyst point of action has remained largely underdeveloped.[3] This is probably due to the inherent difficulties of achieving remote stereoinduction, as a close spatial contact between the chiral catalyst and the reaction site is generally required.[4] Herein, we describe an effective method to carry out a catalytic vinylogous DA reaction with high control over the remote stereochemistry. This transformation relies upon the LUMO-lowering activation of the more distant double bond of α,β,γ,δ-unsaturated cyclic ketones **1** (Figure 1). Specifically, we used chiral Brønsted acid catalysis[5] to increase the tendency of the distant γ,δ-olefinic moiety in **1** to react as a chiral dienophile, an activation principle that has never served to induce vinylogous reactivity to date. The reaction

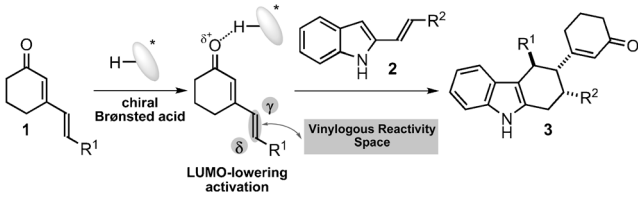

Figure 1. Design of a Brønsted acid catalyzed asymmetric vinylogous Diels–Alder reaction.

with 2-vinylindoles **2**, which can readily participate in [4+2] cycloaddition processes as electron-rich dienes,[6] allowed the direct synthesis of stereochemically dense tetrahydrocarbazoles **3**[7] with very high regio-, diastereo-, and enantioselectivity.

We began our investigations by examining the reaction between cyclic 2,4-dienone **1a** and styryl-1*H*-indole **2a** (Table 1). The choice of substrates was based on our previous experiences with vinylogous reactivity.[8] We recently established that cinchona-alkaloid-based primary amines of type **A**[9] can condense with β-substituted cyclic dienones **1**, which facilitates the formation of an extended iminium ion intermediate while lowering the LUMO energy level of the distant unsaturated π system. The resulting activated vinylogous iminium ion activation allowed for δ-site-selective and enantioselective nucleophilic 1,6-additions[8a] and vinylogous cascade transformations to be realized.[8b] As the same activation principle underlies the Diels–Alder chemistry, we tested the ability of quinidine derivative **A** to catalyze this model reaction in an asymmetric vinylogous fashion (entries 1 and 2). Unfortunately, this catalytic system was ineffective, and provided the desired product **3a** only with poor yield and stereoinduction. However, the vinylogous DA reaction is amenable not only to aminocatalysis, but also to a different activation mode. We found that a Brønsted acid[10] could promote the reaction by effectively activating the carbonyl moiety of dienone **1a**.[5] An array of chiral 1,1′-bi-2-naphthol (BINOL)-derived phosphoric acids[11] were screened as catalysts for the model reaction. Commercially available **4d** was the best catalyst, as its use led to the formation of product **3a** with complete control over the relative configuration and 94% *ee* (entry 6).[12] The more acidic[13] chiral phosphoramide **4e**[10a] induced an appreciable level of stereo- and regioselectivity, but could not parallel the efficacy of **4d** (entry 7). A control experiment confirmed that the Brønsted acid catalyst is needed for the DA reaction to occur (entry 8), while protection of the N–H indole moiety in **2** greatly decreased the stereoselectivity of the process (entry 9). Mechanistically, the last result is consistent with a specific

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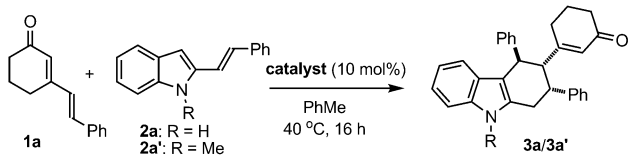
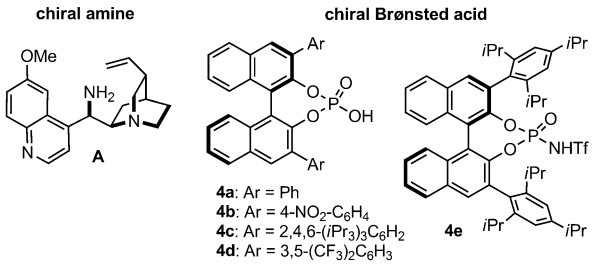
Table 1: Explorative studies.[a]



Entry	Catalyst	R	Conv.[b] [%]	d.r.[c]	*ee*[d] [%]
1[e]	**A**	H	< 5	n.d.	n.d.
2[e]	**A**	Me	55	1:1	27
3	**4a**	H	20	> 20:1	77
4	**4b**	H	40	> 20:1	79
5	**4c**	H	< 5	n.d.	n.d.
6	**4d**	H	74	> 20:1	94
7	**4e**	H	67	> 20:1	81
8	–	H	< 5	n.d.	n.d.
9	**4d**	Me	55	2:1	5
10[f]	**4d**	H	88[g]	> 20:1	94

[a] Reactions performed on a 0.05 mmol scale for 16 h with a catalyst (10 mol%), **2a** or **2a'** (1.2 equiv), and $[\mathbf{1a}]_0 = 0.25$ M in PhMe. [b] Conversion of **1a** determined by ^{1}H NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as the internal standard. [c] d.r. determined by ^{1}H NMR analysis of the crude reaction mixture. [d] *ee* determined by HPLC analysis on a chiral stationary phase. [e] Performed at 60 °C with **A** (20 mol%) and TFA (30 mol%) as the acid co-catalyst. [f] **4d** (5 mol%), **2a** (1.5 equiv), $[\mathbf{1a}]_0 = 0.5$ M, 48 h. [g] Yield of isolated **3a**. n.d. = not determined, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

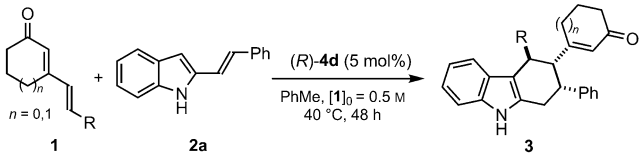


and crucial interaction between substrate **2** and the catalyst, which productively adds to the acid-induced activation of the enone (see below for further discussions).

During a second round of optimization it was found that the use of 5 mol% of phosphoric acid **4d**, a slight excess of **2a** (1.5 equiv), and stirring in toluene at 40 °C for 48 hours provided adduct **3a** with excellent conversion and selectivity (entry 10; 88%, > 20:1 d.r., 94% *ee*). These reaction conditions were thus chosen for evaluating the synthetic potential and the generality of the vinylogous DA reaction. This method is synthetically useful, as a slightly higher efficiency was observed when running the model reaction on a 1 mmol scale (Table 2, entry 1).

A wide range of substituents at the δ-position of the dienone are compatible with the catalytic system. Different substitution patterns at the aromatic moiety were well tolerated, regardless of the electronic properties of the substituents, as the corresponding adducts **3** were obtained in good yields and with enantioselectivities of ≥ 90% *ee* (entries 1–7). The synthesis of furyl derivative **3h** (entry 8) confirmed that a heteroaryl framework can be included in the

Table 2: Scope of the vinylogous DA reaction: variation of the cyclic 2,4-dienone.[a]



Entry	R	*n*	**3**	Yield[b] [%]	*ee*[c] [%]
1[d]	Ph	1	**3a**	86	97
2	4-F-C_6H_4	1	**3b**	70	92
3	4-Cl-C_6H_4	1	**3c**	84	92
4	3-Cl-C_6H_4	1	**3d**	78	92
5[e]	2-Br-C_6H_4	1	**3e**	80	93
6	4-Me-C_6H_4	1	**3f**	86	92
7[f]	4-MeO-C_6H_4	1	**3g**	63	90
8	3-furyl	1	**3h**	78	88
9	Me	1	**3i**	85	89
10	Ph	0	**3j**	60	91

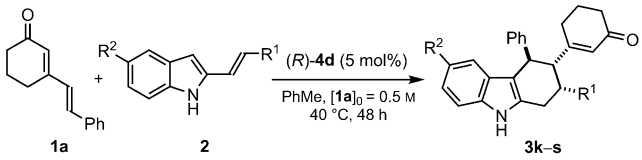
[a] Reactions performed in air, without any precautions to exclude moisture, on a 0.1 mmol scale with **2a** (1.5 equiv). For all of the reactions, a d.r. of > 20:1 was inferred by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated **3** after purification by column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 1 mmol scale. [e] **4d** (10 mol%). [f] 72 h.

final product. Remarkably, this transformation can be extended to include substrates that bear an aliphatic substituent (R = Me, entry 9). Furthermore, a five-membered cyclic scaffold was a competent dienophile of this vinylogous DA reaction, providing the corresponding cycloadduct **3j** with high stereocontrol and a slightly decreased chemical yield (entry 10). As a limitation of this system, acyclic 2,4-dienones did not react at all under the optimized reaction conditions. From a synthetic standpoint, it is worth mentioning that for all of the reactions described in Table 2, products **3** were selectively formed as single diastereomers (complete control over the relative stereochemistry). Crystals that were obtained for compound **3e** (entry 5) were suitable for X-ray crystallographic analysis. Thus, the stereochemical outcome of the Diels–Alder reaction as well as the absolute configurations of the three stereogenic centers could be established.[14]

We then evaluated the generality of this transformation by varying the structure of 2-vinylindole **2**, which is the diene component of the vinylogous DA reaction (Table 3). In general, different substitution patterns on the aryl ring that is attached to the exocyclic double bond (R^1 = aryl) were well tolerated (entries 1–5), although electron-withdrawing groups required the use of 10 mol% of catalyst for synthetically useful chemical yields (entries 1–3). The same behavior was observed for electron-withdrawing or -donating groups at the 5-position of the indole core (entries 6–8), the latter being more reactive towards the vinylogous cycloaddition pathway.

Importantly, the exocyclic double bond could also bear an aliphatic substituent (R^1 = Me; entry 9). In this case, a slightly modified procedure was needed: The diene was added portionwise to prevent a tandem homo-Diels–Alder cyclization/aromatization reaction of **2**.[15] This experiment afforded

Table 3: Scope of the vinylogous DA reaction: variation of the 2-alkenylindole.[a]



Entry	R^1	R^2	3	Yield[b] [%]	*ee*[c] [%]
1[d,e]	4-Cl-C_6H_4	H	**3k**	64	93
2[d,e]	4-Br-C_6H_4	H	**3l**	53	92
3[d]	2-Br-C_6H_4	H	**3m**	95	90
4	4-Me-C_6H_4	H	**3n**	74	93
5	3,5-$(MeO)_2$-C_6H_3	H	**3o**	94	95
6[d,e]	Ph	Cl	**3p**	80	92
7	Ph	Me	**3q**	70	93
8[e]	Ph	MeO	**3r**	59	92
9[d,f]	Me	H	**3s**	61	99

[a] Reactions performed on a 0.1 mmol scale using **2** (1.5 equiv). For all of the reactions, a d.r. of >20:1 was inferred by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated **3** after purification by column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] **4d** (10 mol%). [e] 72 h. [f] Diene **2** was added portionwise to the reaction mixture; using the standard procedure, **3s** was isolated in only 20% yield.

the corresponding adduct **3s** with an excellent enantiomeric excess (99% *ee*, >20:1 d.r.).

We then focused on the mechanism of the transformation. As alluded to above, the decrease in stereoselectivity that is observed when the N–H group of diene **2** is protected (Table 1, entry 9) could suggest the requirement for a key interaction with the Brønsted basic (P=O) moiety of the catalyst **4d**, alongside a concomitant Brønsted acid activation of the carbonyl group of dienophile **1** (P–OH···O=C). We have performed a nonlinear effect (NLE) study[16] of the model reaction to examine whether the optical purity of catalyst **4d** directly correlated with the optical purity of product **3a**.[17] A significant and positive NLE was observed, as shown by the convexity of the curve in Figure 2a, which indicates that more than one molecule of the chiral acid **4d** is likely to be involved in the transition state of the enantiodifferentiating step. A mechanistic model that accounts for these experimental observations is proposed in Figure 2b.[18]

One peculiar feature of this catalytic asymmetric vinylogous DA reaction is that it provides direct and rapid access to tetrahydrocarbazoles **3** while preserving an α,β-unsaturated system. This functional group could be used as a suitable chemical handle for easily increasing the molecular and stereochemical complexity of the products by simple follow-up transformations. To illustrate this synthetic potential, the cyclohexenone moiety of **3a** was stereoselectively converted into epoxyketone **5** by means of a protection/epoxidation sequence (Scheme 1a). Furthermore, we could perform a palladium-catalyzed Suzuki–Miyaura cross-coupling with tetrahydrocarbazole **3m** without requiring an additional protection step, which led to product **6** (Scheme 1b).

In summary, we have developed a highly stereo- and regioselective vinylogous Diels–Alder reaction that is catalyzed by a commercially available chiral phosphoric acid. A range of structurally diverse complex tetrahydrocarbazoles could be synthesized with high chemical yield and excellent stereoselectivity. It was revealed that cyclic dienones can be activated towards a cycloaddition pathway by means of phosphoric acid catalysis. Furthermore, it was demonstrated that the synthetic utility of the Diels–Alder reaction can be extended to include a vinylogous reactivity space.

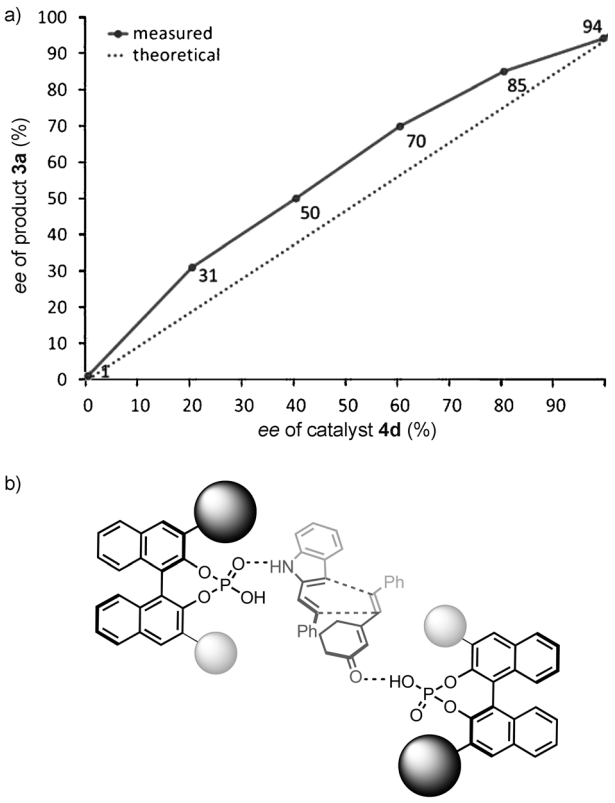
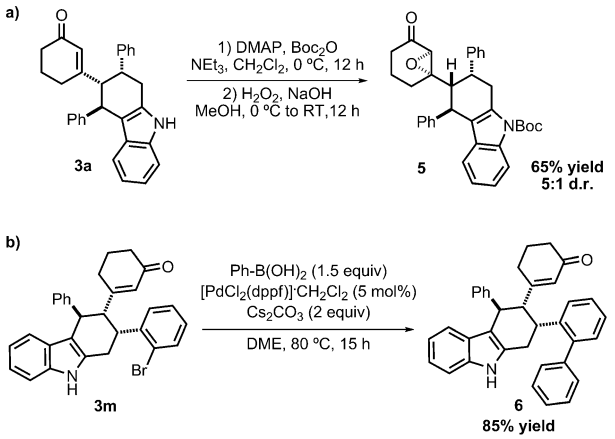


Figure 2. a) NLE study. b) Proposed stereochemical model.



Scheme 1. Synthetic manipulations of the DA adducts. Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, DME = 1,2-dimethoxyethane, dppf = diphenylphosphinoferrocene.

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